REMARKS

Claims 1-5, 9 and 12-23 are pending in the above-identified application. Claim 1 has been amended to focus on exemplified compounds, for which experimental data exists, as shown in Table A at page 11 of the specification, as well as closely related analogues thereof. With the changes to claim 1, the proviso portion thereof has become obsolete. Consistent changes to the dependent claims have also been made. In method claim 18, the list of diseases has been supplemented with "secondary hyperparathyroidism" and "secondary hyperparthyroidism associated with renal failure", which find full support in original claim 22.

Request for Entry of Claim Amendments

It is requested that the changes to the claims be entered of record, since these changes reduce the number of claims and at least place the present application into better form for consideration on appeal, should an appeal be necessary, under 37 CFR 1.116(b).

Unity of Invention and Election of Species Requirements

Applicant respectfully maintains a traversal of the Unity of Invention and Election of Species Requirements for the same reasons stated in Amendment filed August 24, 2009, which reasons are deemed repeated herein.

Issues under 35 USC 112, Second Paragraph

Claims 1-17 have been rejected under 35 USC 112, second paragraph as being indefinite because of the term ethylene in the proviso of claim 1. This portion of claim 1 has been deleted with the above claim changes, such that the basis for this rejection no longer exists. It is requested that this rejection be withdrawn.

Issues under 35 USC 112, First Paragraph

Claims 1-17 have been rejected under 35 USC 112, first paragraph as allegedly failing to satisfy the enablement requirement. This rejection is traversed. It is submitted that the presently amended claims cover compound examples or close analogues supported by experimental data. In this regard, note Table A at page 11 of the specification where claimed compounds are shown

to exhibit *in vitro* PTH suppressive effects and *in vivo* calcemic activity. The Examiner has not cited any objective information in support of the conclusion that any compounds within the present claims would not be expected to exhibit these properties. Also, it is not understood why a table on page 38 is referenced on page 5 of the Office Action, as no table exists on this page. Thus, it is requested that this rejection be withdrawn.

Issues under 35 USC 103(a)

Claims 1-17 have been rejected under 35 USC 103(a) as being unpatentable over Gao '208 (US 6,028.208).

Claims 1-17 have been rejected under 35 USC 103(a) as being unpatentable over Grue-Sorensen '577 (WO 95./02577), Binderup '855 (WO 91/00855), Onisko et al. (Tetrahedron Letters, No. 13, pp. 1107-1108, 1977), and Norma et al. (Vitamin D Basic Research and its Clinical Application, Proc. Of the Fourth Workshop on Vitamin D, Berlin, West Germany, Feb. 1979, pp. 1257-1259).

The above rejections are traversed based on the following reasons.

Distinctions over Gao '208

The Examiner asserts that Gao '208 teaches compounds which suggest or embrace the compounds of the present invention. Applicant respectfully disagrees. Gao '208 claims vitamin D_3 derivatives which require a substituted (C_5-C_7)carbocyclic ring, as at least X and/or Y must be different from hydrogen. Of the claimed compounds in Gao '208, only formula [1]+[1a] or formula [1]+[1b] may constitute an ethenylene group (when A and B express a single bond) between C-20 and the carbocyclic ring as in the present invention. However, the compounds of the present invention do not include substituted (C_5-C_7)carbocyclic rings. Further, Gao '208 fails to disclose or suggest to one skilled in the art that the described compounds should be modified to a different structure, let alone to the structure of the presently claimed compounds. The Examiner fails to cite any evidence that would suggest to one skilled in the art to modify the compounds of Gao '208 for any particular reason. Consequently, significant patentable distinctions exist between the present claims and Gao '208 such that the above rejection must be withdrawn.

Distinctions over Grue-Sørensen '577

Grue-Sorensen '577 discloses a group of specific vitamin-D derivatives with antiproliferative properties, wherein hydroxy containing compounds (X = OH) are preferred (page 2 lines 33-34). Grue-Sorensen '577 fails to disclose or reasonably suggest any of the presently claimed compounds. The suggested use of the disclosed compounds in the treatment of hyperparathyroidism (page 7 lines 14-19) is purely speculative. Grue-Sorensen '577 fails to disclose any data concerning *in vitro* PTH secretion or any other results or evidence which demonstrate the usefulness of the compounds in the treatment of hyperparathyroidism. By viewing the teaching of Grue-Sorensen '577 in its entirety, it is clear that the motivation of making the vitamin-D derivatives disclosed therein was solely to obtain compounds with antiproliferative properties and not to make compounds for the treatment of hyperparathyroidism.

No relationship between structure and *in vivo* calcemic activity are disclosed in Grue-Sorensen '577. In fact, Grue-Sorensen '577 only discloses that two specific compounds have a low calcemic effect without giving any teaching on how to structurally modify vitamin D derivatives in order to obtain compounds which have a reduced calcemic effect. More specifically, the relationship between a low calcemic effect and the blocking of the C-25 position is neither explicitly disclosed, nor can be deduced from the overall teaching of Grue-Sorensen '577.

Experimental evidence to show superior calcemic efficiency of the compounds according to the present invention in comparison with the compounds known from the prior art may be seen with reference to the experimental evidence present in Grue-Sorensen '577 in the table on page 6, lines 1-7. The calcium metabolism values of compound 101 and 102 (0.2 and 0.015 respectively) can be directly compared to the values in table A in the present application by multiplying by 100 ($\Rightarrow$ 20% and 1.5%). The test used for determining the values in the present invention and in Grue-Sorensen '577 are identical and all values are determined relative to $1\alpha,25(OH)_2 D_3$ (i.e. Calcitriol). Hence the calcemic activity is more than twice as low and even up to over twenty times as low for compounds of the present invention compared to compound 101 in Grue-Sorensen '577 when taken relative to Calcitriol. Compound 101 is the preferred compound of Grue-Sorensen '577, see e.g. page 6 lines 26-29. For compound 102 in Grue-

Sorensen '577 the calcemic activity is somewhat lower and at a level closer to the compounds of the present invention. This compound shows no benefits compared to the two reference examples (calcipotriol and EB1089) concerning the ratio between the proliferative effect and the calcemic activity and compound 102 is only highlighted for the high acid stability which is of relevance for oral administration.

There are no hints in Grue-Sorensen '577 how to structurally modify the compounds in order to suggest any of the compounds of the present invention. Grue-Sorensen '577, in fact, discloses that only one compound (in two enantiomeric forms) has been tested, in the direction of obtaining compounds showing a significant calcemic effect, and at the same time showing a sufficiently high s-HPT suppressive effect as shown for the compounds of the present invention. Only a speculative suggestion to this use is given. In particular there are no hints in Grue-Sorensen '577 pointing towards compounds according to the present invention to be favourable in providing compounds showing an even better suppression of the calcemic effect than compounds according to Grue-Sorensen '577. Thus, significant patentable distinctions exist between the present claims and Grue-Sorensen '577 such that the above rejection based on this reference must be withdrawn.

Distinctions over Binderup '855

Binderup '855 is only directed to specific vitamin-D derivatives with anti-inflammatory and immunomodulating effects as well with antiproliferative properties. Binderup '855 is completely silent about a suppressive effect on the secretion of the parathyroid hormone (PTH) of the compounds disclosed therein. Binderup '855 teaches (page 5 line 36 – page 6 line 16) that some vitamin-D derivatives disclosed therein with an incorporated conjugated polyene system in the side chain have a greater selectivity in favour of the potent effects on cell differentiation/proliferation or interleukin production and action contra the effects on calcium metabolism. Thus the calcemic effect is described in relative terms, which means that the calcemic effect may still be unreduced provided that the pharmacological effects distinct from the present application are large enough. More specifically, any relationship between a low calcemic effect and the blocking of the C-25 position is neither explicitly disclosed, nor can be deduced from the overall teaching of Binderup '855.

A person skilled in the art would learn from Binderup '855 that some vitamin-D derivatives with an incorporated conjugated polyene system in the side chain are useful for certain diseases, e.g. proliferative diseases. A person skilled in the art would not expect vitamin-D derivatives which are structurally related to Binderup '855 to have a suppressive effect on the secretion of the parathyroid hormone (PTH) and/or that said vitamin-D derivatives have a low calcemic effect due to the fact that they cannot be hydroxylated in the C-25 position *in vivo*. The compounds in Binderup '855 are focused on potent effects on cell differentiation/proliferation, which is particularly relevant for diseases like psoriasis and cancer. The mechanisms associated with these are distinct from mechanisms related to s-HPT suppressive effects.

Binderup '855 is completely silent about any parathyroid hormone suppressing effect. The compounds according to Binderup '855 further require a hydroxy radical present on the side chain. This hydroxy radical is usually believed to play an essential role for certain cell differentiation/ proliferation activities, in particular in disorders like psoriasis or cancer.
A person skilled in the art would find no hints in Binderup '855 that vitamin D analogues structurally related to compounds of the present invention may be expected to show an inhibitory effect on the production of the parathyroidea hormone and simultaneously a particular low calcemic effect. Thus, significant patentable distinctions exist between the present claims and Binderup '855 such that the above rejection based on this reference must be withdrawn.

Distinctions over Onisko et al.

The compounds of the present invention are clearly distinct from those disclosed in Onisko et al. since the compounds having the most structural similarity to the present compounds, i.e. compounds 3 and 13 of Onisko et al., both contain an aliphatic carbon atom in the side chain attached to C-20. In contrast, in the compounds of the present invention the carbon atom in the side chain attached to C-20 cannot be aliphatic.

Further, Onisko et al. describes the synthesis of vitamin D derivatives which differ structurally from those of the present invention and which might be inhibitors of a mixed-function liver oxidase. Onisko et al. is silent about a suppressive effect on the secretion of the parathyroid hormone (PTH) of the compounds disclosed therein. Onisko et al. does not mention the problem of the calcemic effect of vitamin-D derivatives at all. A person skilled in the art would learn from Onisko et al. that vitamin-D derivatives with altered side chains that cannot be

hydroxylated at C-25 are potential inhibitors of a mixed-function liver oxidase. A person skilled in the art would not expect vitamin-D derivatives which are structurally closely related to Onisko et al. to have a suppressive effect on the secretion of the parathyroid hormone (PTH) and/or that said vitamin-D derivatives have a low calcemic effect due to the fact that they cannot be hydroxylated in the C-25 position *in vivo*.

It is important to notice that a person skilled in the art who reads Onisko et al. would restrain from using vitamin-D derivatives as drugs which cannot be hydroxylated at C-25, especially not for long-term medical treatment, since Onisko et al. teaches that vitamin-D derivatives closely resembling the natural substrate are potential inhibitors of a mixed-function liver oxidase. A person skilled in the art will expect that this inhibition will result in a blocking of the biosynthetic pathway of the synthesis of natural 25-hydroxyvitamin D_2 or D_3 which will ultimately have a negative effect on calcium metabolism. Thus, significant patentable distinctions exist between the present claims and Onisko et al. such that the above rejection based on this reference must be withdrawn.

Distinctions over Norman et al. et al.

Norman et al. et al. discloses the synthesis of a number of vitamin D analogues. However, Norman et al. fails to disclose any compounds falling within the scope of the present claims wherein substituent A is hydroxyl (-OH). Thus, Norman et al. fails to disclose or suggest any of the presently claimed compounds. Moreover, Norman et al. fails to disclose any calcemic or PTH suppressive effects of any of the described compounds, such that there fails to be any basis for a motivation to one skilled in the art to modify the compounds of Norma et al. in an attempt to obtain the presently claimed compounds. Thus, significant patentable distinctions exist between the present claims and Onisko et al. such that the above rejection based on this reference must be withdrawn.

Failure of Alleged Combination of Cited References to Suggest Invention

In addition to the above, it is submitted that the attempt to allege obviousness based on the alleged combination of all of the above references still fails. The above distinctions with respect to chemical structure and properties are very significant. There is simply no reasonable evidence in the present record to suggest to one skilled in the art that modifying the various

compounds described in these references to obtain the presently claimed compounds would lead to any reasonable success. Consequently, even hypothetically combining these various references falls short of suggesting the present invention.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Should there by an outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Andrew D. Meikle , Registration No. 32,868 at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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Attachments